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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/405,032	09/24/1999	WILLIAM J. BOYLE	A-378-CIP2C4	9035

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	17

DATE MAILED: 06/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/405,032	BOYLE ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-67 and 69-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-67 and 69-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 September 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Q. Janice Li, at Group Art Unit 1632.

Continued Prosecution Application

The request filed on 1/13/03 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09405,032 is acceptable and a CPA has been established. An action on the CPA follows.

The preliminary amendment filed with the CPA has been entered as paper #14. Claim 68 has been canceled, claim 67 has been amended, and claims 69-76 are newly submitted. Claims 61-67 and 69-76 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment and response to pending claims will not be reiterated. The arguments in paper #14 are moot in view of new grounds of rejection.

Priority

This application claims the benefit of U.S. applications 09/132,985, now pending; 08/771,777, now abandoned; 08/706,945, now patented, and 08/566,788, now allowed.

Applicants should amend the appropriate section of the specification to indicate the status of the parent application.

Specification

The abstract is objected to because it does not reflect the scope of the invention that the instant claims are drawn to, i.e. administering an expression vector encoding and expressing osteoprotegerin in a mammal. Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 61-67 and 69-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Given the broadest reasonable interpretation, the claims are directed to a therapeutic method for treating bone loss in a mammal comprising administering to the mammal *any* expression vector expressing *any* OPG with/*without* the ligand-binding and Fc region via *any* route of administration. With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. As such, the invention properly encompasses a method of gene therapy for diseases associated with bone loss, such as osteoporosis. When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable

interpretation that is consistent with the specification. As such, "a method for treating bone loss in a mammal", will be evaluated by the standard as whether a therapeutic effect is or can be achieved by the claimed method steps.

The original claims 43-45 and current claims are drawn to a method for regulating the OPG level or treating bone loss in a mammal comprising administering to the mammal a nucleic acid encoding OPG. In view of the disclosure in the specification, the original disclosure teaches nucleic acids and expression vectors for expressing osteoprotegerin, variants, and fragments thereof *in vitro* (Specification, pages 16-22), the specification teaches methods of using polypeptides as pharmaceutical compositions for treating bone loss (Specification, pages 32-36), and the specification teaches a method of making a transgenic mouse having integrated into its genome a nucleic acid sequence encoding osteoprotegerin operatively linked to regulatory elements (Specification, example 3). Although example 3 of the specification subtitled "systemic delivery of OPG in transgenic mice", the expression vector was delivered by nuclear transfer to single-cell embryos, which have not developed into a mammal and do not possess the characteristics of a mammal, accordingly, the method of making a transgenic mouse could not be used as the support for presently claimed invention.

Applicants rely on a Declaration (paper #8) and a post-filing publication (*Bolon et al*, 2001, Exhibit C) as support for instantly claimed invention, however, since the original disclosure is silent regarding the instantly claimed subject matter, a later filed declaration could not supplement the essential element that is missing from the specification. The Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific starting material **or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

It is acknowledged that the Declaration (paper #8) and a post-filing publication (*Bolon et al*, 2001, Exhibit C) provided certain evidence regarding the instantly claimed subject matter. They disclosed experiments performed on a mouse ovariectomy model of osteoporosis, wherein adenoviral vectors were used to deliver OPG to mice by tail vein injection and wherein only administering Ad-OPG-Fc achieved a sustained circulating OPG in a mammal.

However, the Declaration and Exhibit C could not support the full scope of the claims because *Bolon et al* teach that sustained expression only observed in mice receiving Ad-hOPG-Fc, whereas serum levels of OPG were rapidly declined in mice receiving Ad-hOPG or AdmOPG. Apparently, *Bolon et al* teach that simply administering an expression vector encoding and expressing OPG could not achieve a therapeutic effect for treating bone loss.

The Declaration and the *Bolon* publication teach the use of an adenoviral vector for OPG delivery, but fail to teach whether *any* expression vector encoding and expressing OPG-Fc could achieve the sustained levels of OPG, thus, the claims rely on

the levels of the skilled in the art. In view of the state of the art in vector technology, several different vector systems are in use for somatic gene transfer in vivo. These include DNA (either naked or complexed), RNA virues (retroviruses), and DNA viruses (adenovirus, adenoassociated virus, herpesvirus and poxvirus). Each system has perceived advantages and disadvantages, which influence their selection for current or projected clinical applications. For example, adenoviral vector is efficient in cell entry and wide range of host cells, but highly immunogenic and remain episomal, difficult to obtain long-term stability, thus better suited for use in vaccination or transient gene expression; transfection of retroviral vector is limited to dividing cells; AAV requires replicating adenovirus (helper virus) to grow and has very limited insert size. Herpes are highly immunogenic and the transgene is shut down within one week after infection for a variety of target cells, (*Robbins et al*, Pharmacol Ther 1998;80:35-47, entire article, sections 2.2, 2.3 particularly) therefore, they would not be suitable for long-term delivery of therapeutic supplemental proteins, such as OPG or insulin. Herpes and pox viruses are also highly immunogenic. Naked DNA is extremely inefficient in entry, and no mechanism for persistence or stability. (*Orkin et al,* Dec. 1995, pages 21-23, 30-32). The specification only teaches plasmid vectors for *in vitro* expression of OPG and fails to teach how to overcome the art known hurdles for systemic delivery to a mammal of various vectors encompassed by the claims. In fact, *Bolon et al* teach, long after the effective filing date of this application, "STUDIES USING A MORE SUITABLE VECTOR ARE UNDER WAY TO ACHIEVE A MORE REALISTIC, IMPROVED GENE THERAPY APPROACH" (last sentence of the publication, emphasis added). Evidently, the instant disclosure is insufficient to support

the full scope of the claims. It would have required undue experimentation for the skilled artisan intending to practice the instant invention.

The Declaration and Exhibit C could not support the full scope of the claims because they teach intravenous injection of the adv, but fail to teach whether *any* route of administration would deliver the vector encoding and expressing OPG-Fc to the target cells in vivo so that to achieve the sustained circulating OPG levels, thus, again the claims rely on the levels of the skilled in the art. In view of the state of the art, vector targeting is a crucial issue for in vivo gene therapy. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. At the time of the effective filing date of instant application, *Crystal* (1995, Science, Vol. 270, page 404-410) teaches, "AMONG THE DESIGN HURDLES FOR ALL VECTORS ARE THE NEED TO INCREASE THE EFFICIENCY OF GENE TRANSFER, TO INCREASE TARGET SPECIFICITY AND TO ENABLE THE TRANSFERRED GENE TO BE REGULATED" (page 409). *Miller et al* (1995, FASEB J., Vol. 9, pages 190-199), acknowledge various vector system available in the art, then teach, "NO SINGLE DELIVERY SYSTEM IS LIKELY TO BE UNIVERSALLY APPROPRIATE, FOR INSTANCE, THE REQUIREMENTS OF GENE THERAPY FOR CYSTIC FIBROSIS ARE GREATLY DIFFERENT FROM THOSE OF CANCER" (1st paragraph, page 190). "ONCE AGAIN, TARGETING AT THE LEVEL OF THE VECTOR HAS NOT YET BEEN PARTICULARLY WELL DEVELOPED; HENCE, LIPOSOME OR VIRAL-MEDIATED DELIVERY OF THE CFTR GENE TO AIRWAY EPITHELIAL CELLS OF CF PATIENTS HAS RELIED LARGELY ON THE LOCALIZED DELIVERY OF THE VECTORS DIRECTLY TO THE AFFECTED TISSUES" (1st paragraph, page 198). *Deonarain* (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ABILITY TO TARGET A GENE TO

A SIGNIFICANT POPULATION OF CELLS AND EXPRESS IT AT ADEQUATE LEVELS FOR A LONG ENOUGH PERIOD OF TIME" (page 53, first paragraph). *Baylink et al* (Mol Med Today 1999 Mar;133-40) teach, long after instant filing date, "WE AND OTHERS HAVE FOUND THAT BOTH DIFFERENTIATED BONE CELLS AS WELL AS UNDIFFERENTIATED STROMAL CELLS, ARE SOMEWHAT RESISTANT TO GENE TRANSFER. HOPEFULLY, THIS PROBLEM WILL BE RESOLVED IN THE NEAR FUTURE AS GENE DELIVERY METHODS IMPROVE" (right column, page 138). The specification only teaches intravenous injection, fails to teach whether any other route of delivery could deliver the vector to desired target cells and whether sustained circulating OPG levels could be achieved, thus, fails to teach how to overcome the aforementioned difficulties in the art. Accordingly, the instant disclosure is insufficient to support the full scope of the claims. It would have required undue experimentation for the skilled artisan intending to practice the instant invention.

The nature of the invention being gene therapy, the state of the art was not well developed at the time of present effective filing date. For example, *Orkin et al.* (NIH Report, 1995 Dec) reviews the infant state of the art of gene therapy at the time the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; and 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor

definition of biochemical or disease endpoints (pages 1-2). Years after the reference publication date and the instant filing date, the general status of gene therapy art has not significantly changed. Perhaps no one else in the field could summarize the state of the art better than *French Anderson,* who (Hum Gene Ther 2002;13:1261-2) teaches recently that the real situation in practicing gene therapy is much more complex than simple principle that taught in a gene therapy class. "AN ANALOGY MIGHT BE PUTTING AN ASTRONAUT ON THE MOON. NASA CAN DRAW PICTURES OF A SPACECRAFT, WITH ROCKET ENGINES AND A CAPSULE CONTAINING ASTRONAUTS, GOING FROM THE EARTH TO THE MOON. BUT IN FACT, THERE ARE HUNDREDS OF CRITICAL STEPS, ALL OF WHICH MUST WORK SMOOTHLY AND EFFICIENTLY FOR THE WHOLE MISSION TO BE SUCCESSFUL...EVERY SYSTEM MUST BE HIGHLY SOPHISTICATED IN ORDER TO ENSURE SUCCESS. SO, TOO, WITH THE GENE THERAPY" (Section 1, page 1261). Even the achievement applaud by the author of the article, i.e. the successful story in Alain Fischer's X-SCID trial, was shadowed lately because the retroviral vector used in the trial has lead to the cancerous state of the targeted host cells.

Therefore, it is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential of gene therapy, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. However, the specification fails to provide any guidance regarding the essential elements needed for practicing the instantly claimed invention. Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *in vivo* gene expression at therapeutic levels, in particular for the treatment of

any and all diseases associated with bone loss, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to the breadth of the claims directed to *any OPG, any expression vector and any route of administration*, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 61-67, and 69-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 61-67 and 69-76 are vague and indefinite because claims 61 and 69 are incomplete. The claimed method provides for treating bone loss in a mammal, however, there is no positive step or recitation that clearly relates to the preamble indicating that the goal of the invention is resolved.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 61, 65-67, 69, and 73-76 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 11, and 12 of U.S. Patent No. 6,284,740. Although the conflicting claims are not identical, they are not patentably distinct from each other because they both drawn to a method comprising administering to a mammal a nucleic acid encoding and expressing OPG for treating bone loss (or increase bone density).

The processes of the present application and the cited patent differ one from the other in the preamble recitation and in that the present claims recite "an expression vector" rather than "a nucleic acid encoding osteoprtegerin". However, the recited vector is composed of nucleic acids and performs the same function.

Accordingly, the claimed processes in the copending and the present application are obvious variants, and the inventions as claimed are co-extensive.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
May 28, 2003

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